PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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File 81642/02
17 OCT 2005
Frank B. Dehn & Co.
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WRITTEN OPINION OF THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rule 66)

Date of mailing *(day/month/year)*	13.10.2005
Applicant's or agent's file reference 27.14.81642/002	**REPLY DUE** **within 2 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/004341	13.10.2004	13.10.2003

International Patent Classification (IPC) or both national classification and IPC
A61K38/29, A61P3/10

Applicant
CREATIVE PEPTIDES SWEENEN AB et al.

1. ☒ The written opinion established by the International Searching Authority:
   ☒ is ☐ is not
   considered to be a written opinion of the International Preliminary Examining Authority
2. This second report contains indications relating to the following items:
   - ☒ Box No. I Basis of the opinion
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application
3. The applicant is hereby **invited to reply** to this opinion.

   When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(e).
   How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.
   Also: For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*. For an informal communication with the examiner, see Rule 66.6. For an additional opportunity to submit amendments, see Rule 66.4.
   If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
4. The final date by which the international preliminary report on patentability (Chapter II of the PCT) must be established according to Rule 69.2 is: 13.02.2006

DUE DATES NOTED
13/12/05

Name and mailing address of the international preliminary examining authority:
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WRITTEN OPINION OF THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

International application No.
PCT/GB2004/004341

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this opinion is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-21	as originally filed

Sequence listings part of the description, Pages

22, 23	as originally filed
24-31	received on 21.02.2005 with letter of 17.02.2005

Claims, Numbers

1-9	received on 11.07.2005 with letter of 07.07.2005

Drawings, Sheets

1/3-3/3	as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

WRITTEN OPINION OF THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 3

because:

☒ the said international application, or the said claims Nos. 3 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search opinion has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See supplemental sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

International application No.
PCT/GB2004/004341

Box No. V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,3
	No:	Claims	2,4-9
Inventive step (IS)	Yes:	Claims	1,3
	No:	Claims	2,4-9
Industrial applicability (IA)	Yes:	Claims	1,2,4-9
	No:	Claims	3

2. Citations and explanations:

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☒ furnished subsequently to this Authority for the purposes of search and/or examination

   ☒ received by this Authority as an amendment on

2. ☒In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 3 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Documents

1.1. The following document (cited in the application) is referred to in this communication:

D5: Sima A A F; Zhang W; Sugimoto K; Henry D; Li Z; Wahren J; Grunberger G: "C-peptide prevents and improves chronic Type I diabetic polyneuropathy in the BB/Wor rat"; Diabetologia 2001; Vol. 44 (7), 889-897

2. Novelty

2.1. D2 teaches a pharmaceutical composition comprising C-peptide for administration to a patient 1 to 6 times during the course of a day (page 9, line 19-24). D2 explicitly states that **sustained release formulations are preferably given at longer intervals**, e.g. 1 to 2 times a month or every three month.

Consequently, the composition of present claim 2 cannot be considered novel in view of D2.

2.2. Newly cited document D5 discloses a pharmaceutical composition comprising C-

peptide together with at least one pharmaceutically acceptable carrier or excipient. The composition does not include the presence of release rate-controlling agents.

Thus, the subject-matter of present claim 2 cannot be considered novel in view of D5 since the **product itself** is identical. The intended use (for administration as a once daily dose, for the treatment of diabetes or microvascular complications of diabetes) of the product does not establish novelty to the product *per se*.

2.3. Thus, the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 2 and the hereto dependent claims 4-9 is not new in the sense of Article 33(2) PCT.

2.4. Document D1 teaches a pharmaceutical **delayed-release** formulation containing human proinsulin C-peptide and its use for treating diabetes or complications of diabetes.

Document D3 relates to a composition comprising C-peptide of proinsulin and polyunsaturated fatty acids.
The daily dose of these compounds may not exclude the administration of long acting preparations or depot preparation once (or more times) in a day. However, this disclosure is in relation to the treatment of cancer and **not diabetes**.

D4 refers to **depot forms** of proinsulin C-peptide, N-0923 or levodopa.

Thus, the subject-matter of claims 1 and 2 is new in the sense of Article 33(2) PCT.

3. Inventive step

3.1. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 2 and 4-9 does not involve an inventive step in the sense of Article 33(3) PCT (see lack of novelty under point 2.3.).

3.2. Claims 1 and 3:

Document D4, which is considered to represent the most relevant state of the art, discloses depot formulations comprising proinsulin C-peptide as a once daily dose for the treatment of microvascular diabetic complications.

The subject-matter of claim 1 (and 3) of the present application differs from document D4 in that **no release rate-controlling** agents are present.

In the light of the present claims, description and having regard to the prior art, the problem to be solved by the above claims can be formulated as 'provision of an improved method for treating diabetes and/or microvascular diabetic complications'.

The solution proposed in claim 1 (and 3) of the present application can be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

C-peptide is known to have a relatively short half-time. Due to the short half-life of C-peptide, prior art disclosures several days doses, a continuously administered dose or delayed release formulations.

However, the inventors of the present application have surprisingly found that C-peptide given in a once daily dose can be used to treat diabetes (even in the absence of any release rate-controlling agents or continuous administration).

The prior art does not provide any indication that would prompt the skilled person to use a C-peptide formulation (without any release rate-controlling agents or continuous administration) as a medicament for once daily administration for the treatment of diabetes, thus rendering the invention of claim 1 and 3 non-obvious.

4. Method of treatment

For the assessment of the present claim 3 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to

the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.